PATENT
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Joost VAN NEERVEN	)	Group Art Unit: 1641
	)	
Serial No.: 09/467,901	)	Examiner: Pensee T. Do
	)	
Filed: December 21, 1999	)	Confirmation No.: 2936
	)	
For: A METHOD OF DETECTING AND/OR QUANTIFYING A SPECIFIC IGE ANTIBODY IN A LIQUID SAMPLE	)	

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 41.41

In support of the Appeal Brief filed on March 7, 2006, and in reply to the Examiner's Answer dated June 30, 2006, Appellant presents this Reply Brief.

I. Introduction

In this Reply Brief, Appellant responds to comments and arguments made by the Examiner that extend beyond those previously made in prosecution. This limits Appellant's response to the rejection of claims 1-5, 8-14, 16, and 21-23, and specifically, the Examiner's Answer at page 6, lines 17-20 and page 8 to page 11, line 11.

The remaining portion of the Examiner's comments at page 3 to page 6, line 17 and from page 11, line 12 to page 12, line 15 are very similar to statements made in the

Advisory Action dated September 8, 2005, but for the exception of a few additional citations to the references discussed. See the Examiner's Answer and pages 2-5, 9, 10, and 12 of the Advisory Action. As such, the statements do not advance this prosecution process and, because Appellant has already addressed each one in its Appeal Brief, Appellant will not consume the Board's time by re-addressing them.

Regarding the rejection of claims 6 and 17-20, the Examiner once again offered no new commentary on this rejection (see Advisory Action at pages 5, 6, and 10-12) and thus failed to address Appellant's statements in its Appeal Brief. For the sake of completeness, however, Appellant provides herein a brief summary of Appellant's arguments against this rejection as detailed in the Appeal Brief.

Finally, it should be noted that the Examiner's summary of Appellant's position broadly oversimplifies the argument. And in some instances, the Examiner appears to misapprehend the point altogether.

II. Obviousness Rejection in view of Johansen, Johnson, and Frank 2

The Examiner maintains her rejection of claims 1-5, 8-14, 16, and 21-23 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Pat. 6,087,188 (Johansen) in view of U.S. Patent 6,034,066 (Johnson) and U.S. Patent 6,060,326 (Frank 2). As explained in the Appeal Brief, the Examiner combines these references by suggesting that it would have been obvious to use the IgE receptors allegedly taught in Johnson and Frank 2 to measure IgE according to the method of Johansen. See Appeal Brief at pages 9 and 10. Appellant respectfully disagrees.

Johnson teaches nothing about using CD23 in a method to detect physiologically active IgE antibodies in a sample. Johnson further does not teach any method steps, but rather focuses on identifying a cysteine protease (Der p I) that can cleave cell-bound CD23 to form soluble CD23. See col. 3, lines 43-54. The difference here is that soluble forms of CD23 (sCD23) lead to increased production of IgE antibodies (see col. 2, lines 50-57), which in turn lead to increased sensitivity to allergens. See col. 3, lines 33-37. In an effort to reduce this sensitivity, the inventors of Johnson also identified Der p I inhibitors. See col. 9, line 25 to col. 11, line 62. A reference that focuses on a protease that regulates levels of IgE has no nexus to a method of detecting or quantifying IgE. Thus, since Johnson is not relevant here, only Johansen and Frank 2 remain. Appellant addresses these references with regard to claims 1-5, 8-14, 16, and 21-23 below.

A. Motivation to Combine

1. The Examiner's Central Rejection

Perhaps in response to Appellant's comments the Examiner confuses motivation to combine, providing several new arguments that combine Johansen, Frank 2, and Johnson. In her first argument, the Examiner asserts that Johansen teaches the "generic assay steps" of the present invention. It is not clear to Appellant what the Examiner means by the phrase "generic assay steps." For the purposes of responding to the Examiner's argument, however, Appellant will refer to the Examiner's description of Johansen's teaching at page 3 of the Examiner's Answer. Johansen allegedly teaches a method of detecting an antibody in a sample comprising forming a solid phase complex by mixing the following reagents: a ligand antigen bound to biotin, the sample, an antibody directed against the antibody to be detected and bound to

paramagnetic particles, and a chemiluminescent acridinium compound bound to avidin or streptavidin. See Examiner's Answer at page 3. According to the Examiner, Johansen's method continues by separating the solid phase from the liquid phase and concludes by analyzing the solid phase for the presence of the chemiluminescent complex. *Id.* The Examiner then describes Johnson as teaching that a CD23 is an IgE receptor that bind to IgE antibodies associated with allergic, anti-parasitic, and chronic immune responses, citing col. 2, lines 26-30 in the reference. *Id.* at page 8.

Combining the alleged teachings of Johansen and Johnson, the Examiner concludes that the skilled artisan would be motivated to use the CD23 receptor of Johnson in place of the capture antibody in Johansen because Johansen allegedly teaches detecting IgE antibodies and because Johnson teaches that CD23 can stimulate the production of IgE antibodies associated with allergic, anti-parasitic, and chronic immune responses. *Id.* Knowing that CD23 binds to IgE antibodies associated with allergic, anti-parasitic, and chronic immune responses, the Examiner reasons, a skilled artisan can assess the level of immune response by quantifying the amount of IgE using CD23. *Id.* The reasoning underlying this argument is flawed on several levels, as Appellant will explain.

2. The Examiner Misstates the Teaching of Johnson

The Examiner's citation to col. 2, lines 26-30 of Johnson does not support the alleged teaching that CD23 is an IgE receptor that binds to IgE antibodies associated with allergic, anti-parasitic, and chronic immune responses. Rather, this citation discusses only the ability of sCD23 to act as a cytokine to increase the production of IgE and IgG4 antibodies. This citation says absolutely nothing about the ability of the cell-

bound CD23 receptor to bind to IgE. Moreover, the combination of an alleged teaching of a method of IgE antibody detection with a teaching that sCD23 can act as a cytokine provides no motivation to use CD23 in an assay to detect physiologically active forms of IgE. And even if the skilled artisan were to begin with the teaching of Johnson, the skilled artisan would not find motivation to select the assay of Johansen in particular from among many possible assay formats in which a CD23 receptor might be used. Thus, the Examiner's citation to Johnson does not motivate the skilled artisan to use the method of Johansen and CD23 as the Examiner suggests.

3. The Goal of the Invention is to Mimic *In Vivo* Interactions, not to Simply Detect All IgE in a Sample

In her second argument, the Examiner again contends that Frank 2 teaches that FcεR binds to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Examiner's Answer at page 8. Without explaining why, the Examiner simply concludes that in light of this alleged teaching the skilled artisan would be motivated to use the receptors of Frank 2 or Johnson in the method of Johansen. *Id.* at pages 8 and 9.

The Examiner's citation to Frank 2 at col. 1, lines 19-34 does not address the sensitivity of FcεR in binding to IgE. And, even if Frank 2 contained the teaching on sensitivity that the Examiner suggests it does, using a reagent with increased sensitivity demonstrates a rationale reflective of the desire to maximize the detection of <u>all</u> IgE in a sample. This goal is directly <u>contrary</u> to the invention's purpose of performing the method in such a way that the cross-reactions that would happen *in vivo* are reproduced. As explained in Appellant's brief, the specification, and elsewhere, the present invention simulates interference from other components in the sample as well,

which gives a truer account of available IgE within the system, and does not simply provide maximum IgE detection. Regarding cross-reactivity, col. 1, lines 27-29 of Frank 2 explains that "anti-IgE antibodies . . . can cross-react with other antibody idiotypes, such as gamma isotype antibodies." This statement discusses a property of anti-IgE antibodies, not FcεR. Thus, the alleged teachings of Frank 2 that the Examiner relies upon to support a motivation to combine Johansen and Frank 2 are simply not in the Examiner's citations.

As Appellant explained in the Appeal Brief, the invention provides a measurement of IgE that reflects the ability of the IgE to exert its effector functions through binding to the IgE receptor and mimicking *in vivo* interactions between the receptor, the IgE antibody, and the antigen to which the IgE antibody binds. Johansen does not even use IgE receptors, and therefore makes it unlikely that one skilled in the art would look to its teaching, especially in view of a number of other possible assay formats discussed in Frank 2, as a foundational method with which one combines other references to create the present invention.

Frank 2 , though, allegedly uses a canine IgE receptor, but teaches a method in which the receptor is fixed to a solid support or the antigen is fixed to a solid support such as a microtiter dish. See Frank 2 at col. 11, lines 28-30 and col. 13, lines 23-29. Even if Frank 2 taught detection of IgE without fixing a reagent to a solid support, this reference considers methods including immobilizing the receptor to a solid support as the preferred way to carry out the invention of Frank 2. For example, col. 10, lines 39-41 describe immobilization of captured IgE via immobilization of a capture molecule (i.e., a receptor) onto a solid support. The Examiner suggests that Johansen teaches

an anti-IgE antibody bound to paramagnetic particles, which could be in suspension rather than fixed to a solid support as preferred in Frank 2. Thus, the skilled artisan would not find motivation in either reference to pick the method of Johansen in particular from among several assay formats in which the FcεR might be used to detect IgE and perform the assay in such a way as to mimic *in vivo* interactions.

4. Detecting the Presence of T Cells and B Cells in a Sample is Irrelevant to the Invention

In her third argument, the Examiner relies on alleged teachings in Frank 2 and Johnson that FcεR and CD23 bind to various cell types. Examiner's Answer at page 9. Citing col. 8, lines 42-48 of Frank 2 the Examiner contends that this reference teaches that FcεR binds to mast cells, dendritic cells, and basophils. *Id.* Once again, the citation given by the Examiner does not match the alleged teaching that the Examiner describes for that reference. At col. 8, lines 42-48, Frank 2 discusses cells that can produce or be designed to produce IgE antibodies, among them basophils and myeloma cells. As with the other instances above where the Examiner applies her personal knowledge to a reference, akin to hindsight, this discussion has nothing to do with the expression of the FcεR on the surface of cells. Citing col. 1, lines 33-47 of Johnson, the Examiner contends that this reference teaches that CD23 binds to B cells and T cells. *Id.* Likewise, col. 1, lines 33-47 of Johnson discusses in part the cell types that express CD23 on their surface, including B cells and T cells. Expression of a receptor on the surface of a cell, however, is different phenomenon from a cell's ability to bind to a receptor. Finally, the Examiner cites Johnson for the proposition that CD23 influences antigen presentation to B cells and T cells, which determines the degree and nature of immune responsiveness to an antigen. Examiner's Answer at page 9.

Based on these alleged teachings in Johnson and Frank 2, the Examiner concludes that the skilled artisan would be motivated to use CD23 and FcεR to detect IgE according to Johansen's method to compare the abundance of certain IgE antibodies to assess the allergic state of a patient. *Id.* According to the Examiner, the skilled artisan would assess the total IgE that binds to CD23 to study if B and T cells are present in a serum sample. *Id.* Contrary to the Examiner's suggestion, though, serum samples do not normally contain cells. Instead, whole blood contains cells. Serum samples are normally prepared by centrifuging whole blood to remove the cells and retain the fluid component of blood, which contains antibodies. Thus, using a serum sample, as Johansen allegedly suggests, would not facilitate the study of cells normally found in whole blood.

Moreover, the determination of the presence of B and T cells in a sample has nothing to do with detecting the presence of antibodies in a sample. *Arguendo*, even if the Examiner's interpretation of the teachings of Johansen, Johnson, and Frank 2 were correct, a motivation to detect T cells or B cells in a sample does not provide motivation for detecting physiologically active forms of IgE.

Finally, it is not clear how assessing total IgE that binds to CD23 would detect T cells or B cells. As Johnson teaches, CD23 is expressed on several cell types, including T cells and B cells.

For all of these reasons, Appellant contends that none of the Examiner's new arguments provide a motivation to combine the teachings of Johansen, Frank 2, and Johnson.

5. The Examiner's Corollary Rejections

The Examiner also briefly addresses additional arguments presented by the Appellant in its Appeal Brief.

a. Frank 2 Does Not Discuss Human IgE Receptors

First, the Examiner seems to believe that Appellant tried to distinguish the rejected claims from Frank 2 by noting that Frank 2 addresses a canine receptor, FcεR. Appellant agrees that the rejected claims are not limited to the use of human IgE receptors. Appellant merely noted that Frank 2 discusses canine receptors to clarify the record because during the prosecution, the Examiner consistently indicated that Frank 2 taught a human IgE receptor, which was not accurate. See, e.g., Advisory Action dated September 8, 2005, at page 5; Office Action dated April 6, 2005, at page 5; and Office Action dated September 8, 2004, at page 5.

b. Frank 2 and Johansen Do Not Use the Same Reagents

In a second argument, Appellant explained in the Appeal Brief why Johansen does not teach using the reagents of Frank 2 in its method steps. See Appeal Brief at pages 13-16. During prosecution, the Examiner asserted that a motivation to combine these references existed in the alleged overlap of reagents between the two references. See Office Action dated September 8, 2004, at page 8 and 9. The Examiner now says that Frank 2 and Johansen do not have to use the same reagents. Examiner's Answer at page 10. And the Examiner repeats that if Frank 2 used the same reagents as Johansen, Frank 2 would have been used as the basis of an anticipation rejection of the claims and not for obviousness. *Id.* Because Frank 2 was not used as the basis of an anticipation rejection, however, Appellant logically takes these statements by the

Examiner to mean that the Examiner agrees that Johansen and Frank 2 do not teach the same sets of reagents. Thus, on this level as well, the Examiner has not provided a motivation to combine the teachings of Johansen and Frank 2.

c. "Genus" Refers to the Variety of Assay formats that Might Use a Canine Receptor

In a third argument, Appellant also discussed in its Appeal Brief the Examiner's cite to col. 2, lines 13-17 and col. 8, lines 50-56 of Frank 2. Appeal Brief at pages 14 and 15. The first citation stated that "the invention [of Frank 2] relates to the discovery that purified, high affinity canine Fc epsilon receptor . . . can be used in canine epsilon immunoglobulin (referred to herein as IgE or IgE antibody)- based detection . . . methods and kits," appearing to suggest that FcεR could be used in canine IgE-based detection methods. *Id.* Appellant explained that a general suggestion that an IgE receptor might be used in the genus of detection assays did not suggest its use in the particular method of the invention. *Id.* In her answer, the Examiner has misconstrued Appellant's use of the term "genus," thinking that Appellant used this term to distinguish between canine IgE receptors and human receptors. Examiner's Answer at page 10. On the contrary, Appellant used the term "genus" to describe the variety of detection assay formats in which a canine receptor could be used and that general teaching did not point to a particular assay format such as the one recited in claim 1. Appellant referred to a canine receptor because that is what Frank 2 discusses.

d. An Alleged Overlap of Substrates Between References Does Not Alone Provide a Motivation to Combine

Finally, Appellant discussed the Examiner's citations to two additional passages from Frank 2. See Appeal Brief at pages 15 and 16. The first citation teaches in part

that "a complex can be formed in which one or more members of the complex are immobilized on (e.g., coated onto) a substrate. . . Suitable substrate materials include . . . . particulate materials such as latex, polystyrene, nylon, nitrocellulose, agarose, and magnetic resin." Appellant noted in its brief that other substrates that do not float freely in solution are cited as well, such as a microtiter dish, a plate, a dipstick, a membrane, a filter, a tube, and a dish. Given the complete list of substrates provided in Frank 2, this citation could refer to coating a microtiter plate with canine FcεR as easily as it might refer to coating a particle. Appellant noted that the Examiner has still not explained why out of this list, the artisan would be motivated to choose a particulate particularly when the goal of Frank 2 differs so much from the goal of the present invention.

The Examiner now explains that because Johansen allegedly teaches using a solid phase, such as magnetic particles, and Frank 2 also allegedly suggests using a particulate support such as magnetic particles, the skilled artisan would be motivated to use magnetic particles to eliminate washing steps. Examiner's Answer at page 11. Even if the Examiner's description of these teachings were correct, a potential overlap of one possible type of substrate does not alone motivate the skilled artisan to combine the teachings of both references in a particular way to arrive at the claimed invention. As Appellant has explained in the Appeal Brief, Johansen and Frank 2 differ in the set of reagents used in their assays and the Examiner's statements agree with that conclusion.

In sum, Appellant has demonstrated why none of the Examiner's bases for a motivation to combine the teachings of Johansen, Frank 2, and Johnson are sound. Johansen appears to teach the use of anti-IgE antibodies. And since the Examiner

arguably admits that Frank 2 teaches away from the use of anti-IgE antibodies, there is no motivation to combine these references. Examiner's Answer at page 9. Because the Examiner has not provided a motivation to combine these references, she has not fulfilled her burden of presenting a *prima facie* case of obviousness against claims 1-5, 8-14, 16, and 21-23.

B. Expectation of Success

In the Appeal Brief, Appellant noted that the Examiner had not provided a basis for showing a reasonable expectation of success in combining the references. Appeal Brief at page 16. The Examiner now contends that Johansen teaches using an anti-IgE antibody as a capture reagent in a method to detect IgE, while Johnson and Frank 2 teach using an IgE receptor. Examiner's Answer at page 9. Appellant notes (as above) that Johnson does not teach IgE detection assays at all, and thus, disagrees with the Examiner's proposition. Nevertheless, based upon these alleged teachings, the Examiner reasons that the skilled artisan would have a reasonable expectation of success in replacing Johansen's anti-IgE antibody with an IgE receptor because the skilled artisan knows that the IgE receptor would bind to IgE in a serum sample. *Id.* Regarding Frank 2, the Examiner contends that this reference teaches away from the use of anti-IgE antibodies to act as a capture reagent. *Id.* If Frank 2 teaches away from using anti-IgE antibodies (as compared to IgE receptors), then such a teaching implies that Frank 2 does not consider the two components as functional equivalents. Indeed, this is true. The skilled artisan would not expect the anti-IgE antibody allegedly taught in Johansen and the FcεR allegedly taught in Frank 2 to be interchangeable. Thus,

Appellant contends that the skilled artisan would not have had a reasonable expectation of success in replacing the anti-IgE antibody with an IgE receptor in Johansen's assay.

Appellant unfortunately notes that the Examiner has repeated verbatim from the Advisory Action her insufficient basis for expectation of success, founded in a motivation to combine the references. Compare Examiner's Answer at pages 11-13 to Advisory Action dated September 8, 2005, at pages 9-12. As Appellant explained in the Appeal Brief, the requirements of a motivation to combine and expectation of success are separate components of a *prima facie* case of obviousness. Again, the Examiner inappropriately shifts the initial burden of showing an expectation of success to Appellant by suggesting that Appellant has not pointed to factors that would prevent a successful combination of the references. *Id.* at page 12.

C. Claim 23 and Inherency

Regarding claim 23, the Examiner has now changed the basis underlying the rejection of this claim. In the past, the Examiner rejected claim 23 because the phrase "simulating *in vivo* interactions" was not given patentable weight. See Advisory Action dated September 8, 2005, at page 5, lines 17 and 18. In her Answer, the Examiner now rejects claim 23 because the combined references allegedly teach the same method steps as the claimed invention and therefore, in the Examiner's view, inherently simulate *in vivo* interactions between an IgE antibody, its ligand, and the IgE receptor. See the Examiner's Answer at page 6, lines 17-20. Appellant respectfully disagrees.

Johansen's method appears to include the following steps: (a) mixing an antigen bound to biotin, an anti-IgE antibody bound to paramagnetic particles, a chemiluminescent acridinium compound bound to avidin, and the sample; (b)

magnetically separating the solid phase from the liquid phase; and (c) initiating the chemilumescent reaction and analyzing the solid phase for chemiluminescent activity. See col. 2, line 56 to col. 3, line 2. Frank 2 discloses several assay formats for detecting IgE in a sample. See, e.g., col. 1, line 59 to col. 2, line 1; col. 7, lines 21-27; col. 10, lines 50-58; and col. 11, line 54 to col. 12, line 9. One of these methods appears to entail the following steps: (a) immobilizing an allergen (antigen) to a substrate, (b) contacting the allergen with a sample containing canine IgE, (c) removing non-bound material from the substrate under conditions that retain antigen:IgE complex binding, and (d) detecting the antigen:IgE complex with a canine FcεR molecule. See col. 1, line 59 to col. 2, line 1. Importantly, no combination of steps from Johansen's method and the method of Frank 2 provides the same method steps of the rejected claims. In fact, the skilled artisan would not see how any intercombination of the steps of Johansen and Frank 2 would make sense as a method. Thus, Appellant contends that the combined method steps of Johansen and Frank 2 do not teach the same method steps as the claimed invention and do not inherently simulate *in vivo* interactions between an IgE antibody, its ligand, and the IgE receptor.

Appellant notes that the Examiner's rejection of claims 1-5, 8-14, 16, and 21-23 is based on a substitution, not a combination of steps from the two references. Specifically, the Examiner suggests that it would be obvious to substitute the canine FcεR of Frank 2 or the CD23 receptor of Johnson into the method of Johansen. As Appellant has explained in the Appeal Brief and further below, such a substitution is not proper.

D. Conclusion

The Examiner has not presented a *prima facie* case of obviousness against claims 1-5, 8-14, 16, and 21-23. These claims are not obvious in light of Johansen, Frank 2, and Johnson, and thus, are allowable.

III. Obviousness rejection in view of Johansen, Frank 2 and Arnold

A. Motivation to Combine and Reasonable Expectation of Success

The Examiner rejected claims 6 and 17-20 by applying Johansen and Frank 2, as discussed above, and invoked Arnold for the alleged discussion of a sandwich assay combining an immobilized antibody[1] with a test medium so that antigens will bind to the immobilized antibody. Examiner's Answer at page 7. In Arnold, unbound antigen is allegedly removed in a first separation step after which a labeled antibody is added, thus sandwiching the antigen between the immobilized antibody and the labeled antibody. *Id.* A second separation step then presumably removes any unbound labeled antibody. *Id.* The Examiner combined these references, suggesting that it would have been obvious to add a label molecule after a first separation step and then separate the non-complexed labels in a second separation step using the reagents in Johansen's method as modified by Frank 2. *Id.* The Examiner acknowledged that separation steps are time consuming, but believed that they increase assay "sensitivity" and eliminate cross-reaction between the label and the immobilized antibody. *Id.*

[1] When describing Arnold, the Examiner provides a parenthetical description of the immobilized reagent as an IgE receptor. The citation given by the Examiner, however, does not recite an IgE receptor, it merely discusses an immobilized antibody. Indeed, Arnold does <u>not</u> discuss an IgE receptor at all.

Appellant explained that independent claim 6 recites two separation steps. More importantly, it also shares the features of the invention that lead to simulating the *in vivo* interactions of IgE antibodies: a liquid sample, a free dissolved ligand, an IgE receptor bound to a carrier, and exposure of the ligand to the antibody before exposure to the receptor. The Examiner relied upon Arnold for teaching separation steps, which as Appellant has explained in the Appeal Brief is not the thrust of Arnold. See Appeal Brief at pages 22 and 23. As discussed above in light of the Examiner's new comments, the combination of Johansen and Frank 2 provide neither the requisite motivation to combine these references nor a reasonable expectation of success in doing so. Arnold's discussion of a sandwich assay in the background section of this patent fails to cure these defects.

Arnold considers antibodies more so as reagents for detecting a ligand. See col. 6, lines 58-59. In contrast, the instant invention focuses on detecting physiologically active IgE antibodies in a sample. Moreover, Arnold teaches immobilization of a capture antibody. As such, the interaction between the antibody and the ligand does *not* take place freely in solution. In contrast, as noted above, the ligand of the invention is a free, dissolved ligand that can interact with IgE antibodies in the liquid sample. See Amendment dated September 26, 2003 at page 19. There is no teaching in Arnold suggesting that such an assay could be adapted to detect antibodies, let alone using an antibody receptor that is not immobilized to do it.

If anything, Arnold teaches away from heterogenous assays that use two separation steps. The thrust of Arnold's invention is to develop a method that increases sensitivity over heterogenous assays by avoiding separation steps. Thus, Arnold does

not encourage the use of one separation step, let alone two. When considering the teachings of Arnold in the context of Johansen and Frank 2, the combination of these three references cannot obviate the rejected claims.

Furthermore, Arnold's methods use a label that undergoes a change in stability once a ligand binds. See Arnold, col. 5, lines 7-19. Typical heterogenous assays use labels that do not change in the presence of a ligand, thereby requiring a separation step to remove non-complexed label. *Id.* While Arnold may discuss the use of an optional separation step, it is in the context of decreasing background noise in homogenous assay formats. *Id.* Thus, Arnold's disclosure focuses on homogenous assay formats using special labels, citing time consumption among other reasons as a basis for developing homogenous assays that do no require separation steps as conventional heterologous assays do. See Arnold at col. 5, lines 10-20.

In the Examiner's Answer at page 14, the Examiner repeats her conclusory contention that IgE is detected by the method of Johansen and Frank 2 and the label must have some means for binding to the IgE. According to the Examiner, such means could come in the form of an antibody or a receptor alternatively. *Id.* Accordingly, the Examiner concludes that a skilled artisan would be able to "figure out" which reagent to use and have a reasonable expectation of success in doing so. *Id. Arguendo*, if as the Examiner suggests, antibodies and receptors would work equally well in Arnold's assay then there can be no motivation to make the specific substitution of the receptor for an immobilized antibody while keeping the labeled antibody. The motivation to combine, if any exists, speaks to the motivation to combine all three references cited against the claims. Whether or not Arnold is simply cited for teaching a separation step, there still

must be some nexus that suggests a combination that results in the claimed invention. *See Medichem, S.A. v. Rolabo, S.L.*, 2006 U.S. App. LEXIS 2653, at *14-15 (Fed. Cir. Feb. 3, 2006); M.P.E.P. § 2142 (October 2005).

Finally, the Examiner's assertions that the skilled artisan would know or could "figure out" which reagent to use and have a reasonable expectation of success in doing so represent the Examiner's opinions and are not supported by factual evidence. If the skilled artisan has to "figure out" which reagent to use, then there is independent experimentation or independent thought not provided in the teaching of the asserted art. The combination of Johansen, Frank 2, and Arnold cannot render claims 6 and 17-20 obvious.

B. Conclusion

In sum, Arnold cannot remedy the lack of motivation to combine this reference with Johansen and Frank 2. The Examiner's explanation that the skilled artisan would be motivated to use such separation steps does not address the motivation to combine Arnold with the teachings of Johansen and Frank 2. *Id.* Nor does Arnold remedy the lack of a reasonable expectation of success in combining the references.

As discussed in the rejection based on Johansen, Frank 2, and Johnson, the Examiner has not pointed to a motivation to combine these references or to a reasonable expectation of success in doing so. In the present rejection, the removal of Johnson and the addition of Arnold does not cure these defects. Thus, the Examiner has not met her initial burden of presenting a *prima facie* case of obviousness and the combination of Johansen, Frank 2, and Arnold cannot render claims 6 and 17-20 obvious.

IV. Conclusions

For the reasons set forth above, pending claims 1-6 and 8-23 remain allowable and Appellant requests reversal of the Examiner's rejections against these claims.

To the extent any extension of time under 37 C.F.R. § 1.136(b) is required to obtain entry of this Reply Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136(b), please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

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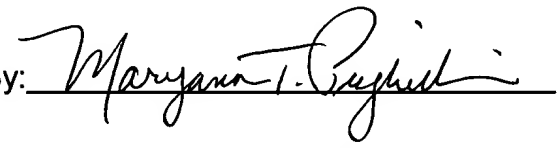
Dated: August 30, 2006

By: 

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